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Respectfully submitted,

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DETOMIDINE HYDROCHLORIDE - A NOVEL IMIDAZOLE-TYPE SEDATIVE-ANALGESIC

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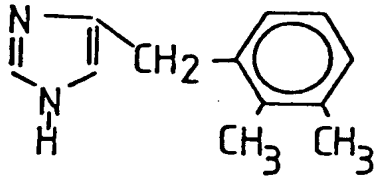
During screening for sedative-analgesic effects of many imidazole-type compounds, detomidine proved to be an extremely potent sedative-analgesic agent for horses and cattle.

DETOMIDINE



ANALGESIC PROPERTIES OF DETOMIDINE

In the preliminary screening test detomidine inhibited carrageenin induced oedema of rats suggesting anti-inflammatory effect. A diuretic action of detomidine was evident. *In vitro* detomidine inhibited the metabolism of arachidonic acid as seen in platelet aggregation inhibition effects as well as depressing effects on prostaglandin synthetase. Thus a peripheral analgesic and anti-inflammatory effect by inhibition of prostaglandin synthesis was evident.

In the hot-plate test of mice, detomidine showed a clear dose-dependent analgesic effect at doses 300-600 µg/kg and in Writhing test at doses 150-600 µg/kg. These doses did not decrease the spontaneous motility of mice, therefore, a true analgesic effect was obvious.

Detomidine did not show any neuromuscular blocking effects as studied using the isolated rat phrenic nerve-hemidiaphragm and chick m. biventer cervicis preparation.

In the hot-plate test and Writhing test detomidine was compared with

morphine on mice. Detomidine was superior to morphine in its analgesic effect in these tests.

The analgesic efficacy of detomidine therefore has two suggestive mechanisms : 1. the anti-inflammatory mechanism based on the inhibition of prostaglandin synthesis ; 2. the effect in the CNS inhibiting transmission of pain impulses. Some of these effects seem to be mediated through an agonistic action on central α_2-receptors.

SEDATIVE PROPERTIES OF DETOMIDINE

In the primary screening studies detomidine showed CNS depression at oral doses of 1 mg/kg in the Irwin screen test in mice. In chicken detomidine was also hypnotic. In rats and mice detomidine did not show true hypnotic properties (general anaesthesia was not obtained by any dose level).

The sedation was demonstrated by a decrease of spontaneous motility of mice at the dose 1500 µg/kg.

The potentiation of barbiturate sleeping-time in mice at doses above 150 µg/kg was a clear demonstration of the CNS depressive potency of detomidine before the sedative behaviour appeared.

SYMPATHOMIMETIC EFFECTS

Detomidine showed sympathomimetic effects like piloerection and exophthalmos in mice and rats. The blood pressure of rats decreased after i.v. doses 10-300 µg/kg but increased at higher doses. Upon cerebroventricular administration of small doses of detomidine, the blood pressure decreased.

Both hypotensive and hypertensive doses effectively decreased the heart rate of rats like the agents traditionally documented as α_2-adrenoceptor agonists (such as clonidine). The sedative effect of detomidine appears at doses which increase blood pressure.

Detomidine did not induce contractions in rat or cow isolated uterus preparations (contraction is typical for xylazine).

PHARMACOKINETICS

Detomidine is rapidly distributed into the whole body after i.m., i.v. or s.c. administration. The maximal concentration in mouse brain (higher than in plasma) was found 0.5 h after i.v. injection. Detomidine was eliminated into urine and feces mainly as three metabolites. The elimination $t_{1/2}$ in rat was 12.7 h, in dog 22.1 h and in calf 20.0 h. Detomidine was well tolerated in all the species studied.

CLINICAL PHARMACOLOGY

In a search for effects on domestic animals, detomidine proved to be extremely good sedative in horses, cattle, sheep and goats (less effective in swine, dogs and cats). Therefore, the clinical pharmacological investigations were performed as doubleblind studies against xylazine on three adult horses and three dairy cows.

The used doses of detomidine were 100-300 µg/kg in horses and 30-150 µg/kg in cows. The administration routes were i.m. and i.v. Xylazine (Rompun^R, Bayer) was used at the recommended doses 400-1200 µg/kg in horse and 50-150 µg/kg in cattle.

A clinical study was run by practizing veterinarians on 109 horses and 103 cows using dose levels of 8-250 µg/kg detomidine for horses and 18-120 µg/kg for cattle. Detomidine induced in 5-15 minutes a sedation leading to easy handling. The i.v. doses had a more rapid onset of action. The animals were tranquillized and sedated but retained the upright position after treatment. The duration of action was dose-dependent, lasting between 1-5 hours. If same doses as recommended for xylazine were used, detomidine had a superior sedative and analgesic potency, especially in horses. In cows the equipotent doses of detomidine and xylazine are comparable. On horses detomidine seemed to be extremely effective. Only 1 per cent dose of xylazine being required to obtain the same effect. Detomidine at sedative doses induced a rapid and dose dependent increase in arterial blood pressure and a consistent bradycardia in horse and cattle. The bradycardia was accompanied by SA and AV-blocks in EEG of the horses. No serious arrhythmias were detected. Respiratory rate was slightly increased in horses and slightly decreased in cattle.

No adverse side effects such as abortions were seen during the studies.

Résumé

Etude des propriétés sédatives et analgésiques chez le cheval et les ruminants d'un dérivé imidazolique : la sétomidine. Les essais pharmacologiques ont d'abord révélé le pouvoir anti-inflammatoire de cette molécule vis-à-vis de l'oedème à la carragénine (rat), de l'agrégation plaquettaire (in vitro), suggérant une inhibition de la synthèse des prostaglandines. Le pouvoir analgésique (test de la plaque chauffante) s'est révélé dose-dépendant (0,3-0,6 mg/kg) et supérieur à celui de la morphine. L'action sédative est manifeste dans le test de criblage d'Irwin (souris), vis-à-vis de l'activité spontanée et dans la potentialisation du temps de sommeil. Enfin, ont été mis en évidence des effets sympathomimétiques (pilo-érection, exophtalmie), en l'absence cependant de tout effet excito-moteur vis-à-vis de l'utérus, comme c'est le cas pour la xylazine.

Le temps de demi-vie est de l'ordre de 20 h chez le veau et 22 h chez le chien (12,7 h chez le rat). Sur le plan clinique, la dose de 0,1-0,3 mg/kg chez le cheval et 0,03-0,15 mg/kg chez la vache s'est révélée très efficace pour obtenir la sédation des animaux sans chute sur le sol ; l'effet qui est immédiat dans le cas de l'injection intraveineuse est observé au bout de 5 à 15 mn dans le cas de l'injection intramusculaire.